IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants	:	Ivan KING and Li-Mou ZHENG
U.S. Serial No.	:	10/738,423
Confirmation No.	:	8783
Filed	:	December 16, 2003
Art Unit	:	1633
Examiner	:	Qian Janice Li
For	:	COMPOSITIONS AND METHODS FOR TUMOR-TARGETED DELIVERY OF EFFECTOR MOLECULES

Law Offices of Albert Wai-Kit Chan, PLLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357

July 11, 2008

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

APPELLANT BRIEF ON APPEAL PURSUANT TO 37 CFR § 41

A Notice of Appeal was filed on May 20, 2008 in connection with the above-identified application. An Appeal Brief is due on July 20, 2008; hence, this Appeal Brief is being timely filed.

The required fee for filing an Appeal Brief is TWO HUNDRED AND FIFTY-FIVE DOLLARS ($255.00) for a small entity. Appellants hereby authorize the Examiner to charge the amount of TWO HUNDRED AND FIFTY-FIVE DOLLARS ($255.00) to Deposit Account No. 50-1891 for payment of the required fees

One copy of the Appeal Brief is filed pursuant to Manual of Patent Examining Procedure, §1205.02.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Vion Pharmaceuticals, Inc. by virtue of an assignment recorded on October 16, 2001, at Reel/Frame 012277/0251.

II. RELATED APPEALS AND INTERFERENCES

No appeals or interferences have been filed to the knowledge of the Appellants, Applicants' undersigned attorney, or the assignee that are related to or would be affected by a decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF CLAIMS

Claims 1-112, and 114 have been canceled. Claims 113, 115-117, 119-124 were rejected; claims 118 and 125 were withdrawn from consideration. Consequently, claims 113, 115-117, 119-124 are currently appealed.

IV. STATUS OF AMENDMENTS

A Final Office Action was issued on December 20, 2007. No further amendments have been filed subsequent to the amendment filed October 22, 2007; therefore, no amendments were filed subsequent to final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 113 is drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises a msbB$^-$ mutant. The present specification discloses a mutant msbB$^-$ *Salmonella* strain VNP20009 (page 74, lines 8-9), and the uses of strain VNP20009 together with cytoxan or cisplatin (page 104, line 1 to page 106, line 20).

Claim 123 is drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of an anti-cancer compound and an effective amount

of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises a msbB$^-$ mutant. The present specification discloses a mutant msbB$^-$ *Salmonella* strain VNP20009 (page 74, lines 8-9), and the uses of strain VNP20009 together with an anti-cancer compound (page 104, line 1 to page 106, line 20).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 113, 115-117, and 119-124 were properly rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (Nature Biotechnology 1999; 17:155-64) (hereinafter "Low") in view of Schachter et al. (Cancer Biotherapy Radiopharmacology 1998; June: 13:155-64) (hereinafter "Schacter").

VII. ARGUMENT

The Final Office action of December 20, 2007 rejected claims 113, 115-117, and 119-124 over the combined disclosures of Low and Schachter. The Final Office action states the following:

(a) Low teaches a method of treating tumors using an *msbB$^-$ Salmonella* mutant which is attenuated and tumor-targeting.

(b) Low teaches that such mutant may be administered to reduce the volume of melanoma solid tumors in a variety of subjects of different species.

(c) Tests conducted by the investigators of the Low reference imply that the aforementioned bacteria can be safe for human use.

(d) Schachter disclosed a routine regimen of chemotherapy comprising the chemotherapeutic agent cisplatin for treating human melanoma, and that the chemotherapeutic regimen had been clinically routine and therefore well-known in the art.

(e) Schachter provides evidence that it is routine to combine chemotherapeutic therapies with newly developed biotherapies, and specifically, in the case of Schachter, a chemotherapy with a biotherapy involving cytokines that regulate the immune system of patients with metastatic melanoma. Schachter therefore supplements Low's deficiencies respecting dual modality of treatment.

(f) Because Schacter also applied the cytokine biotherapy and chemotherapy sequentially, it would have been obvious for a person of ordinary skill in the art to apply the tumor-targeting bacteria of the instant application in a sequential manner with a chemotherapy.

(g) Schacter teaches a need for improvement of conventional chemotherapies with respect to response rate and displays that the response rate of patients is greater when a chemotherapy is used in conjunction with a biotherapy.

Applicants submit that the rejection of the claims is sustained by conclusory statements and an articulated reasoning with a rational underpinning has not been presented to support the legal conclusion as to obviousness.

Claims 113, 115-117, 119-122

The framework for the analysis of obviousness has been settled law. Three factual inquiries must be made to support obviousness:

1) establishing the scope and content of the prior art;
2) establishing the scope of the prior art and the claims at issue; and
3) establishing the level of ordinary skill in the pertinent art.

Last year, the U.S. Supreme Court reiterated the same in KSR International Co. v. Teleflex Inc. and elaborated on the standards for determining obviousness. *See generally* KSR International Co. v. Teleflex, 127 S.Ct. 1727 (2007) (hereinafter "KSR"). The Supreme Court also further iterated that, "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR at 1741 (quoting In re Kahn, 441 F.3d 977, 988 (CA Fed. 2006)).

Following this decision, the USPTO issued supplemental guidelines for examination. *See* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR* v. *Teleflex*, *Inc.*, 72 Fed. Reg. 57526 (October 10, 2007) (hereinafter "Examination Guidelines"). Applicants acknowledge that the USPTO has stated that these

guidelines do not constitute substantive rulemaking and do not have the force and effect of law. Applicants do, however, believe that said guidelines offer evidence that an articulated reasoning with a rational underpinning for obviousness rejection is lacking with respect to the examination of this application.

The USPTO guidelines recite a non-exclusive list of examples of rationales which may be used to articulate a rejection based on obviousness, now at MPEP § 2143. These include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. *See* Examination Guidelines at 57529.

A review of this list suggest that the Examiner has attempted to employ certain of these arguments but the logic of the arguments is flawed, as demonstrated in the following section of this brief.

1. The Examiner's Stated Rationales Fail to Articulate Grounds for a "Reasonable Expectation of Success" or "Anticipated Success" When Combining the Teachings of Schachter and Low, and are Conclusory

In order to establish a *prima facie* case of obviousness in this matter, it must be shown that as of

Appellants' earliest filing date, the combination of Schachter and Low would have provided a reasonable expectation of success in arriving at the claimed subject matter. MPEP 2142 (*citing*, *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). KSR reemphasized this by stating, "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the **anticipated success**, it is likely the product not of innovation but of ordinary skill and common sense." [Emphasis added.] KSR at 1742. As discussed below, the Examiner's Rationales fail to articulate grounds for a reasonable expectation of success or for anticipated success.

It appears that the Examiner has primarily attempted to frame the combination of Schachter and Low as, "Combining prior art elements according to known methods to yield predictable results," or alternatively, as "'Obvious to try' - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success." In the Office Action of December 20, 2007, the Examiner makes the following argument against the applicants:

> Again, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980), wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. [December 20, 2007 Office Action, p. 8.]

The Examiner further states:

> Given the teaching of the prior art compositions of cisplatin and attenuated *Salmonella*-all taught to be useful for the treatment of cancer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of cancer with a reasonable expectation of success. [Emphasis added] [December 20, 2007 Office Action, p. 8.]

And later cites KSR:

> In response to the argument that there is no specific suggestion or teaching in the

> references to combine prior art, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a fining [sic] of obviousness. [...] Here, all the recited elements were known in the art, and hence "THE COMBINATION OF FAMILIAR ELEMENTS ACCORDING TO KNOWN METHODS IF LIKELY TO BE OBVIOUS WHEN IT DOES NO MORE THAN YIELD PREDICTABLE RESULTS." *KSR*, 127 S. CT. AT 1740, 82 USPQ2D AT 1395-96.

However, contained nowhere in the Examiner's rejections is there any rationale that results were "predictable" beyond the conclusory allegation that there would be a reasonable expectation of success when combining an anti-cancer chemotherapy with an anti-cancer biotherapy, generally. *See* December 20, 2007 Office Action, p. 5-6 (stating "*Schachter et al* further supplemented *Low et al* by illustrating it was routine to combine a chemotherapeutic regimen with a newly developed biotherapy in treating solid tumors such as melanoma. [...] [I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the attenuated tumor-targeted mutant *Salmonella* therapy as taught by *Low et al* with a routine chemotherapeutic regimen as taught by *Schacter et al* with a reasonable expectation of success.").

2. A Person of Ordinary Skill in the Art Would Not Have Had a Reasonable Expectation of Success With Respect to the Combination of Low and Schachter As of the Date of Invention

As a means of estimating whether persons of ordinary skill would have perceived a reasonable expectation of success with respect to this combination, a cursory search was performed at the NIH Entrez Pub Med portal. The searches using the terms indicated below were performed as of Appellants' earliest filing date of October 4, 1999 (U.S. Prov. Applications 60/57,500, 60/157,581, and 60/157,637) and compare to a current date, i.e., May 15, 2008.

Search Term	Number of Hits On or Before 10/4/1999	Number of Hits On or Before 5/15/2008
"*Salmonella*" and "cancer"	1817	2320
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A review of all available abstracts from the 156 search results from the combination of "chemotherapy" and "*Salmonella*" and "tumor" pre-dating October 4, 1999 reveals not one instance in which a conventional chemotherapy was used in conjunction with a tumor-targeted *Salmonella* bacterium biotherapy.[1]

[1] While a number of references describe a treatment with Salmonella LPS, they do not reference treatment with a

What the search does reveal instead, is literature displaying the problem of *Salmonella* infection of various different strains in those with weakened immune systems, such as cancer patient populations subjected to chemotherapeutic regimens.[2]

Therefore, given that bacterial infection, and bacterial infection with *Salmonella*, was a well-known occurrence among immune-compromised cancer patients undergoing chemotherapeutic therapy, it would have been particularly counterintuitive to combine a live *Salmonella* bacterium shown to infect tumor-tissue with a conventional chemotherapy at the time of invention. Therefore, there could not have been a reasonable expectation of success respecting the combination of a conventional chemotherapy with the disclosed biotherapy of the instant application.

3. The Stated Need in the Field of Endeavor is Overbroad, the Scope and Content of the Prior Art is Overbroad, and the Obviousness Rationale Fails to Evidence Predictability

Under KSR, "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the element in the manner cited." KSR at 1742. This is echoed in rationale (F) which states that obviousness is present where "Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to

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Salmonella bacterium or an attenuated Salmonella bacterium, in conjunction with chemotherapy. *See* 1) S. Goto et al., Intradermal administration of lipopolysaccharide in treatment of human cancer, 42(4) Cancer Immunol. Immunother. 255-61 (abstract only) (May 1996).; 2) T. Shimizu et al., Combined effects of synthetic lipid A analogs or bacterial lipopolysaccharide with glycosaminylmuramyl dipeptide on antitumor activity against Meth A fibrosarcoma in mice, 14(8) Int. J. Immunopharmacol. 1415-20 (abstract only) (Nov. 1992).; 3) H. Abe, Antitumor effect of LPS immobilized beads, (abstract only) (Jun. 1991).; 4) G.J. Vosika et al., Phase-I study of intravenous modified lipid A, 18(2) Cancer Immunol. Immunother. 107-112 (abstract only) (1984). Additionally, while one other describes synergistic anti-tumor effects of Salmonella mini-cell preparations in conjunction with a chemotherapy, it does not speak to a tumor-infective Salmonella bacterium. *See* S. Kurashige, Synergistic anti-tumor effect of mini-cells prepared from Salmonella typhimurium with mitocycin C in EL4-bearing mice,14(3) Cancer Immunol. Immunother. 202-4(abstract only)(1983).

[2] For examples, *see* 1) J. Trupl et al., Nosocomial bacterial and fungal meningitis in cancer patients, 3(6) Support Care Cancer 385-6 (abstract only (Nov. 1995), describing a case of meningitis caused by Salmonella enteritis; 2) J.L. Beebe & E.W. Koneman, Recovery of uncommon bacteria from blood: association with neoplastic disease, 8(3) Clin. Microbiol. Rev. 336-56 (abstract only)(Jul. 1995), stating that cancer chemotherapy provides a "barrier break" to organisms including Salmonella species; and 3) L.J. Noriega et al., Salmonella infections in a cancer center, 2(2) Support Care Cancer 116-22 (abstract only)(Mar. 1994), citing antineoplastic therapy as a predisposing factor for Salmonella infection, including Salmonella typhimurium.

one of ordinary skill in the art." MPEP § 2143.

Here, the Examiner provides an extremely broad problem to be addressed: "The rationale for the design of the combined therapy was to achieve a higher percentage of a complete response (CR, meaning disappearance of all measurable disease) to drug treatment." Final Office Action of December 20, 2007, p. 5. It is again emphasized that the need (as identified in Schachter) is one of "further improvement of the conventional chemotherapy." *Id.* at 6.

Under the Examiner's rationale, nearly any combination of therapies, however novel their use together might be at the time of invention, would be considered obvious if each separately performed a stated function of decreasing measurable disease. Applicants believe that if an obviousness claim were to succeed on such a broad rationale, experimentation in the chemotherapeutic and biotherapeutic arts would be stifled. Moreover, in the explanation of rationale (F), the MPEP states that, the Examiner should show that the scope and content of the prior art, whether in the same field of endeavor as that of the applicant's invention or a different field of endeavor, included a similar or analogous device (method, or product). Applicants would attest that the devices of the prior art are not to be considered "analogous" simply because both are used to treat cancer (and solid tumors particularly). Applicants attest that the biotherapy of Schachter (i.e. a cytokine molecular therapy of interferon-α and GM-CSF), is too different from the biotherapy technology of the instant invention, i.e. a living, replicating bacteria, to form the basis of an obviousness rejection.

No incentives or market forces are identified beyond the generalized goal of improving chemotherapy and eliminating disease states, and as stated infra, the combination would not have been predictable at the time of invention.

Applicants are aware that under KSR, an analysis by the Examiner of whether there was an apparent reason to combine known elements "need not seek out precise teachings directed to the challenged claim's specific subject matter". KSR at 1741. However, Applicants maintain that the Examiner should show at minimum, more than a general motivation to improve the chemotherapeutic arts, or

to combine chemotherapy with any new biotherapy; instead a motivation to combine a chemotherapy with a tumor-targeted *Salmonella* bacteria should be demonstrated.

Claims 123-124

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2) establishing the scope of the prior art and the claims at issue; and

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Last year, the U.S. Supreme Court reiterated the same in KSR International Co. v. Teleflex Inc. and elaborated on the standards for determining obviousness. *See generally* KSR International Co. v. Teleflex, 127 S.Ct. 1727 (2007) (hereinafter "KSR"). The Supreme Court also further iterated that, "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR at 1741 (quoting In re Kahn, 441 F.3d 977, 988 (CA Fed. 2006)).

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However, contained nowhere in the Examiner's rejections is there any rationale that results were "predictable" beyond the conclusory allegation that there would be a reasonable expectation of success when combining an anti-cancer chemotherapy with an anti-cancer biotherapy, generally. *See* December 20, 2007 Office Action, p. 5-6 (stating "*Schachter et al* further supplemented *Low et al* by

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What the search does reveal instead, is literature displaying the problem of *Salmonella* infection of various different strains in those with weakened immune systems, such as cancer patient populations subjected to chemotherapeutic regimens.[4]

Therefore, given that bacterial infection, and bacterial infection with *Salmonella*, was a well-known occurrence among immune-compromised cancer patients undergoing chemotherapeutic therapy, it would have been particularly counterintuitive to combine a live *Salmonella* bacterium shown to infect tumor-tissue with a conventional chemotherapy at the time of invention. Therefore, there could not have been a reasonable expectation of success respecting the combination of a conventional chemotherapy with the disclosed biotherapy of the instant application.

3. The Stated Need in the Field of Endeavor is Overbroad, the Scope and Content of the Prior Art is Overbroad, and the Obviousness Rationale Fails to Evidence Predictability

Under KSR, "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the element in the manner cited." KSR at 1742. This is echoed in rationale (F) which states that obviousness is present where "Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to

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No incentives or market forces are identified beyond the generalized goal of improving chemotherapy and eliminating disease states, and as stated infra, the combination would not have been predictable at the time of invention.

Applicants are aware that under KSR, an analysis by the Examiner of whether there was an apparent reason to combine known elements "need not seek out precise teachings directed to the challenged claim's specific subject matter". KSR at 1741. However, Applicants maintain that the Examiner should show at minimum, more than a general motivation to improve the chemotherapeutic arts, or

to combine chemotherapy with any new biotherapy; instead a motivation to combine a chemotherapy with a tumor-targeted *Salmonella* bacteria should be demonstrated.

CONCLUSION

In conclusion, it is respectfully suggested that the Honorable Board reverse the appealed rejections as not establishing a *prima facie* case of obviousness. As described at length above, proper application of the methods for determining the motivation to combine the teachings and suggestions of Schachter with those of Low do not rise to the level of *prima facie* obviousness. In large part, the lack of motivation to combine the references is based on the fact that persons of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the appealed claims, as of Appellant's earliest filing date.

Accordingly, reversal of all rejections under § 103(a) is respectfully requested. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

Albert Wai Kit Chan

Albert Wai-Kit Chan
Registration No. 36,479
Attorney for Applicants
Law Offices of Albert Wai-Kit Chan, PLLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357
Tel: (718) 799-1000
Fax: (718) 357-8615
Email:chank@kitchanlaw.com

VIII. CLAIMS APPENDIX

113. (Previously presented) A method of inhibiting the growth of, or reducing the volume of a solid tumor cancer, comprising administering to a subject having a solid tumor cancer an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises an msbB$^-$ mutant.

115. (Previously presented) The method of claim 113 wherein, the solid tumor or cancer is either a lung cancer or colon cancer.

116. (Previously presented) The method of claim 113 wherein the subject is a mammal.

117. (Previously presented) The method of claim 113 wherein the subject is a human.

119. (Previously presented) The method of claim 113, comprising administering an effective amount of cisplatin.

120. (Previously presented) The method of claim 113, wherein the administering of the attenuated tumor-targeted *Salmonella* msbB$^-$ and the administering of the cytoxan or cisplatin are not performed concomitantly.

121. (Previously presented) The method of claim 115, wherein the solid tumor cancer is a lung cancer.

122. (Previously presented) The method of claim 115, wherein the solid tumor cancer is a lung cancer.

123. (Previously presented) A method of inhibiting the growth of, or reducing the volume of a solid tumor cancer, comprising administering to a subject having a solid tumor cancer an effective amount of,

(a) a pharmaceutical composition consisting essentially of an anti-cancer compound and one or more pharmaceutically acceptable carriers, and

(b) an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises an msbB$^-$ mutant.

124. (Previously presented) The method of claim 123 wherein the anti-cancer compound is cisplatin.

IX. EVIDENCE APPENDIX

None

X. RELATED PROCEEDINGS APPENDIX

None